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Matthias Kohlhauer, Lys Darbera, Fanny Lidouren, Mourad Chenoune, Bijan Ghaleh, et al.. Comparative effect of hypothermia and adrenaline during cardiopulmonary resuscitation in rabbits.: Intra-arrest hypothermia and cold saline infusion. Shock, 2014, 41 (2), pp.154-8. 10.1097/SHK.0000000000000083 . inserm-01011114

HAL Id: inserm-01011114

<https://www.hal.inserm.fr/inserm-01011114>

Submitted on 23 Jun 2014

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**Comparative effect of hypothermia and adrenaline
during cardiopulmonary resuscitation in rabbits**

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Running title: Intra-arrest hypothermia and cold saline infusion

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Funding sources: Grant (ABYSS-R12031JJ) from the “Agence Nationale pour la Recherche” (Paris, France). M. Kohlhauer was supported by a grant from the “Région Ile-de-France” (CORDDIM). R. Tissier was recipient of a “Contrat d’Interface INSERM-ENV”.

No conflict of interest

Abstract (250 words)

Introduction: Therapeutic hypothermia was shown to facilitate resumption of spontaneous circulation (ROSC) when instituted during cardiac arrest. Here, we investigated whether it directly improved the chance of successful resuscitation independently of adrenaline administration in rabbits. We further evaluated the direct effect of hypothermia on vascular function *in vitro*.

Methods: In a first set of experiments, four groups of anaesthetized rabbits were submitted to 15 min of cardiac arrest and subsequent cardiopulmonary resuscitation (CPR). The "Control" group underwent CPR with only cardiac massage and defibrillation attempts. Two other groups received cold or normothermic saline infusion during CPR (20 ml/kg of NaCl 0.9% at 4°C or 38°C, respectively). In a last group, the animals received adrenaline (15 µg/kg i.v.) during CPR. In a second set of experiments, we evaluated at 32 vs 38°C the vascular function of aortic rings withdrawn from healthy rabbits or after cardiac arrest.

Results: In the first set of experiments, cardiac massage efficiency was improved by adrenaline but neither by hypothermic nor normothermic saline administration. ROSC was observed in 5/8 animals after adrenaline as compared to 0/8 in other groups. Defibrillation rates were conversely similar among groups (7/8 or 8/8). In the second set of experiments, *in vitro* hypothermia (32°C) was not able to prevent the dramatic alteration of vascular function observed after cardiac arrest. It also not directly modified vasocontractile nor vasodilating functions in healthy conditions.

Conclusion: In rabbits, hypothermia did not exert a direct hemodynamic or vascular effect that might explain its beneficial effect during CPR.

52 **Key Words**

53 Cooling, Cardiac arrest, Ventricular fibrillation, Fluid, Cardiac massage, Animal Study.

54

INTRODUCTION

It is well admitted that therapeutic hypothermia (32°C-34°C) improves the prognosis and the neurologic recovery of comatose survivors after cardiac arrest ¹⁻³. A maximal neurological ⁴⁻⁷ and cardiovascular ⁸⁻¹⁰ protection is obtained when hypothermia is started as soon as possible, e.g., using cold saline infusion during cardiopulmonary resuscitation (CPR). The so-called “intra-arrest” hypothermia was shown to facilitate resumption of spontaneous circulation (ROSC) in rodents and porcine models ^{6, 11}. Two recent observational studies corroborate these results by the demonstration of a higher frequency of ROSC in patients receiving hypothermia through cold saline infusion during CPR as compared to standard care ^{12, 13}.

To our knowledge, the exact mechanism underlying the effect of therapeutic hypothermia on ROSC remains still unknown but several hypotheses have been made. In pigs, hypothermia was shown to improve the response to defibrillation attempts ^{6, 11} and decrease the amount of adrenaline required to achieve ROSC ⁶. Hypothermia was also reported to improve systemic hemodynamics by increasing arterial resistances ¹⁴. In animal models, the influence of hypothermia on vessel function and hemodynamics was however investigated when combined to adrenaline, which could alter the exact role played by therapeutic hypothermia ^{6, 15-17}. The aim of the present study was to investigate the intrinsic vascular effect of hypothermia during CPR. Accordingly, we investigated the effect of therapeutic hypothermia induced by cold saline infusion on cardiac massage efficiency in rabbits without adrenaline administration. In order to determine the real effect of hypothermia versus that of fluid loading, we compared cold saline to warm saline infusion. We finally included a group with adrenaline administration alone, as a positive control of efficient CPR. Our end-points were cardiac massage efficiency assessed by hemodynamic parameters, rate of defibrillation success

80 and ROSC occurrence. In addition, we also examined the direct effect of hypothermia
81 (32°C vs 38°C) on the vascular response of isolated vessels after cardiac arrest in
82 rabbits.

83

MATERIALS AND METHODS

The animal instrumentation and the ensuing experiments were conducted in accordance with French official regulations, after approval by the local ethical committee (ComEth AnSES/ENVA/UPEC n°16).

Animal preparation and cardiac arrest procedure

Male New Zealand rabbits (2.5-3.0 kg) were anaesthetized using zolazepam, tiletamine and pentobarbital (all 20-30 mg/kg i.v.). After intubation and initiation of mechanical ventilation ($FiO_2 = 30\%$), two central catheters were inserted in the carotid artery and jugular vein for measurements of central arterial and venous pressures, respectively. Two electrodes were implanted upon the chest and inserted into the oesophagus. After a period of stabilization, ventricular fibrillation was induced by an alternative current (10 V, 4 mA) between the two electrodes. Mechanical ventilation was stopped throughout the cardiac arrest period. After 15 min of untreated cardiac arrest, CPR was initiated using cardiac massage (~200 beats/min) and restoration of a continuous oxygen flow ($FiO_2=100\%$). Electric attempts of defibrillations (10 J/kg) were started at the 3rd min of CPR and repeated every 2 min until ROSC, which was considered as an organized cardiac rhythm with a systolic arterial pressure above 40 mmHg during at least 1 min.

Experimental protocol

In addition to basic life support and electric attempts of defibrillation, rabbits were randomly assigned to one experimental group (Figure 1A). The Control group did not receive any additional procedure. In the “Saline 4°C” and “Saline 38°C” groups, the animals received 20 ml/kg of NaCl (0.9% at 4°C or 38°C, respectively) from the 1st to the 3rd min of CPR. The last group received bolus administrations of adrenaline (15 µg/kg i.v.) every 2 min until occurrence of ROSC. In the Control group, as well as in “Saline 4°C”

and “Saline 38°C” groups, no any vasopressor drug was used. Resuscitation efforts were stopped after 10 min of unsuccessful CPR or in case of haemoptysis.

Throughout the protocol, rectal, oesophageal and tympanic temperatures were monitored using thermal probes (Harvard Apparatus, Paris, France). Hemodynamic parameters were also continuously recorded using external electrocardiogram, arterial and venous blood pressures in the right carotid and jugular vein, respectively. The difference between arterial and venous pressures was calculated with the data acquisition software HEM version 3.5 (Notocord, Croissy-sur-Seine, France). End-tidal CO₂ concentration in the expired air (EtCO₂) and blood oxygen saturation (SpO₂) were continuously assessed. The primary end-point of the study was the percentage of animals achieving ROSC in each group. Defibrillation success and hemodynamic parameters were secondary end-points.

In vitro analysis of vascular function

Additional rabbits were anaesthetized and intubated as described above. They were randomly submitted to a “Sham” procedure without any cardiac arrest or to 15 min of untreated ventricular fibrillation as previously described. In the latter case, animals were resuscitated using cardiac massage, electric attempts of defibrillation and adrenaline administration. After ROSC, the animals were monitored during 6 hours with constant adrenaline infusion in order to avoid hypotension if necessary. If necessary, anesthesia was maintained using pentobarbital administration. Animals were then euthanized and the descending thoracic aorta was removed and cleaned of connective tissues. Aorta rings were mounted in isolated vessels chambers, as previously described¹⁸. After 120 min of equilibrium under resting tension of 2 g, the chamber temperature was randomly adjusted at either 32°C or 38°C. Thirty minutes later, the response to increasing concentrations of noradrenaline was evaluated (0.3, 1 and

3 $\mu\text{mol/L}$). The endothelial-dependent and independent relaxation was then assessed using acetylcholine (0.1 mmol/L) and sodium nitroprusside (0.1 mmol/L), respectively. The experiments were repeated at two levels of temperature (32 or 38°C).

Statistical analysis

Data were expressed as mean \pm SEM. Temperatures, hemodynamic and *in vitro* parameters were compared between the different groups using a two-way ANOVA for repeated measures followed by a Fisher LSD post-hoc analysis. The time to achieve successful defibrillation were compared between groups using a log-rank test. A similar analysis was used for the time to ROSC. The rate of successful defibrillation and ROSC were compared using a Chi-square test. The corresponding Kaplan-Meier curves were drawn. Significant differences were determined at $p \leq 0.05$.

RESULTS

In vivo investigations

Thirty-two rabbits were randomly included in the different groups (n=8 in each group). As illustrated in Figure 1B, the esophageal, tympanic and rectal temperatures were not significantly different among groups at baseline. During CPR, a significant and expected decrease was observed for oesophageal and tympanic temperatures in the “Saline 4°C” group as compared to all other groups. The rectal temperature was still not significantly different among the 4 groups.

As shown in Table 1, hemodynamic parameters, SpO₂ and EtCO₂ were not different among groups at baseline. After the onset of CPR, cardiac massage efficiency was greater in the “Adrenaline” group as compared to the 3 other groups as evidenced by a significant increase in arterial blood pressure and in the maximal difference between arterial and venous pressures. These parameters were conversely not significantly modified in the two “Saline” groups as compared to the “Control” group.

As illustrated in Figure 2, electric attempts of defibrillation led to a high and similar rate of successful defibrillation in all groups (7/8 animals in the “Control”, “Saline 4°C” and “Adrenaline” groups; 6/8 in the “Saline 38°C” groups, respectively). However, no animal elicited successful ROSC in the “Control”, “Saline 4°C” and “Saline 38°C” whereas 5/8 rabbits achieved ROSC in the “Adrenaline” group. In the “Saline 38°C” group, resuscitation efforts were interrupted in 3 rabbits after occurrence of haemoptysis.

In vitro investigations

Experiments were conducted in 15 and 14 aorta rings sampled from 3 rabbits under sham condition and 4 others after cardiac arrest, respectively. In the rabbits submitted to cardiac arrest, the total dose of adrenaline administered *in vivo* before euthanasia was 990±179 µg/kg. As illustrated in Figure 3A, the noradrenaline administration induced a

171 concentration-dependent contraction *in vitro* in all groups. This effect was however
172 significantly attenuated after cardiac arrest as compared to sham condition but this was
173 not modified by temperature (32 vs 38°C). The endothelium-dependent relaxation in
174 response to acetylcholine was also significantly altered after cardiac arrest but remained
175 unchanged regardless the chamber temperature (figure 3B). Endothelium-independent
176 relaxation after sodium nitroprusside administration was maximal and identical in all
177 conditions.

DISCUSSION

The present study demonstrates that hypothermia induced by cold saline infusion neither affected defibrillation success, ROSC frequency nor cardiac massage efficiency in rabbits. Pure fluid loading through warm saline infusion was also inefficient whereas adrenaline administration improved cardiac massage efficiency and rate of ROSC. To our knowledge, this is the first study to specifically address the effect of cold or warm fluid loading with no concomitant administration of adrenaline during CPR in animals. Previous studies rather investigated the role of hypothermia “on top of” adrenaline administration ^{6, 8, 11, 15, 19-22}. In our experimental conditions, mild hypothermia did also not affect vessel reactivity in isolated aorta after cardiac arrest.

The most important finding of this study is the lack of effect of hypothermia on ROSC occurrence when applied alone, *i.e.*, without adrenaline administration. In a recent review, Scolletta et al. showed that hypothermia conversely facilitates ROSC in pigs and rodents when it was combined to adrenaline administration ¹⁹. The rate of ROSC was for example improved with cold blanket cutaneous application ¹¹, cold saline infusion ⁶, hypothermic liquid ventilation ^{15, 20}, trans-nasal evaporation cooling ^{21, 22} or endovascular cooling ⁸ in pigs. Interestingly, this was often attributed to defibrillation facilitation during hypothermia ^{6, 11}. As example, Boddicker *et al.* demonstrated that hypothermia dramatically improved the chance of defibrillation in a swine model of refractory ventricular fibrillation ¹¹. Menegazzi *et al.* also demonstrated that hypothermic CPR reduced the decay of ECG waveforms and subsequently improved the rate of successful defibrillation ⁶. In our study, it was not possible to show a similar benefit since the rate of successful defibrillation was virtually maximal in Control conditions.

Another apparent discrepancy is the lack of effect of hypothermia on cardiac massage efficiency, as observed in a previous pig study ¹⁵. Indeed, neither cold saline infusion nor normothermic fluid loading were able to affect hemodynamic parameters during CPR. This could be in part related to the proper effect of fluid loading which could compromise the direct effect of cardiac hypothermia. Indeed, Riter et al. showed that a load-independent cooling strategy (hypothermic liquid ventilation) could improve coronary perfusion pressure during CPR as compared to cold saline infusion. In our study, the appearance of several cases of haemoptysis also suggests a poor tolerance of fluid loading after warm saline infusion. It was not possible to directly assess coronary perfusion pressure in the present study since this is technically challenging in the rabbit model ^{15, 23, 24}. The difference between arterial and venous central pressures could however be considered as an indirect evaluation. In accordance with the previous findings of Riter et al. ¹⁵ in pigs, it was not modified by hypothermic fluid loading, this is actually in accordance.

In the present study, we did not investigate the combined effect of hypothermia and adrenaline *in vivo* as the latter was too efficient by itself. Any improvement in the rate of ROSC would therefore be hard to evidence in such experimental conditions. We proposed to address this issue *in vitro* through the determination of the temperature effect on the vascular response to adrenergic stimulation. These experiments clearly showed a lack of effect of temperature (32 vs 38°C) on the vascular response to noradrenaline, while cardiac arrest dramatically altered vascular function. The latter result could be either attributed to tachyphylaxis and desensitization after adrenaline administration or to an actual vascular dysfunction, as described regarding microcirculation in patients after cardiac arrest ²⁵. With lower temperatures, Mustafa and Thulesius interestingly showed that profound hypothermia (27°C and 10°C) altered

the response to noradrenaline of isolated carotids arteries ¹⁶. The cutaneous application of low temperatures (e.g., ice packs) is also well known to induce superficial vasoconstriction ^{14, 26}.

In conclusion, cold saline infusion in the absence of adrenaline administration did not improve ROSC occurrence in rabbits. One could speculate that fluid loading hidden the beneficial effect of temperature reduction in this model.

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Table 1 : Hemodynamic parameters

	Baseline				Cardiopulmonary resuscitation (t=3 min)			
	Control	Saline 4°C	Saline 38°C	Adrenaline	Control	Saline 4°C	Saline 38°C	Adrenaline
<u>Heart rate (beats/min)</u>								
	256±7	260±9	254±8	260±8	244±7	242±8	245±11	251±7
<u>Arterial pressure (mmHg)</u>								
Max	103±7	104±4	102±3	107±4	62±2	57±4	51±3	92±11 *
Mean	83±10	84±7	89±4	90±5	26±2	30±7	25±1	51±6 *
Min	72±10	70±4	78±4	79±5	2±2	6±2	6±1	19±9 *
<u>Venous pressure (mmHg)</u>								
Max	6±1	6±1	4±1	5±1	57±10	38±9	54±13	60±11
Mean	4±1	5±1	3±1	3±1	22±3	18±4	17±4	16±4
Min	2±1	3±1	1±1	1±1	-1±1	2±2	-4±3	-3±2
<u>Maximal difference between arterial and venous pressure (mmHg)</u>								
	101±6	98±4	99±3	106±4	36±4	28±8	33±5	69±11 *
<u>End-tidal CO₂ concentration in the expired air (mmHg)</u>								
	43±7	38±2	40±2	35±5	21±7	19±3	18±2	19±2
<u>Blood oxygen saturation (%)</u>								
	100	99±1	100	99±1	76±9	71±5	79±4	78±6

*, p<0.05 vs all other groups

LEGEND OF FIGURES

Figure 1: Experimental protocol and body temperatures.

Panel A: Schematic representation of the experimental protocol. Animals were randomly assigned to the following groups: "Control", "Saline 4°C" (20 ml/kg of cold NaCl 0.9% i.v.), "Saline 38°C" (20 ml/kg of warm NaCl 0.9% i.v.), or "Adrenaline" (boluses of 15 µg/kg i.v.).

Panel B: Body temperatures throughout protocol in the different groups.

*CPR, cardiopulmonary resuscitation; Temp., temperature; VF, ventricular fibrillation; *, $p < 0.05$ between "Saline 4°C" and all other groups.*

Figure 2: Rate and frequency of successful defibrillation and resumption of spontaneous circulation (ROSC).

Panel A: Overall frequency of successful defibrillation, ROSC and haemoptysis appearance during cardiopulmonary resuscitation efforts.

Panel B: Rate and frequency of successful defibrillation during cardiopulmonary resuscitation efforts.

Panel C: Rate and frequency of ROSC during cardiopulmonary resuscitation efforts.

**, $p < 0.05$ vs all other groups.*

Figure 3: In vitro investigations at two different temperatures (32 vs 38°C) of the vascular function of aorta rings sampled from healthy rabbits (Sham groups) or after cardiac arrest

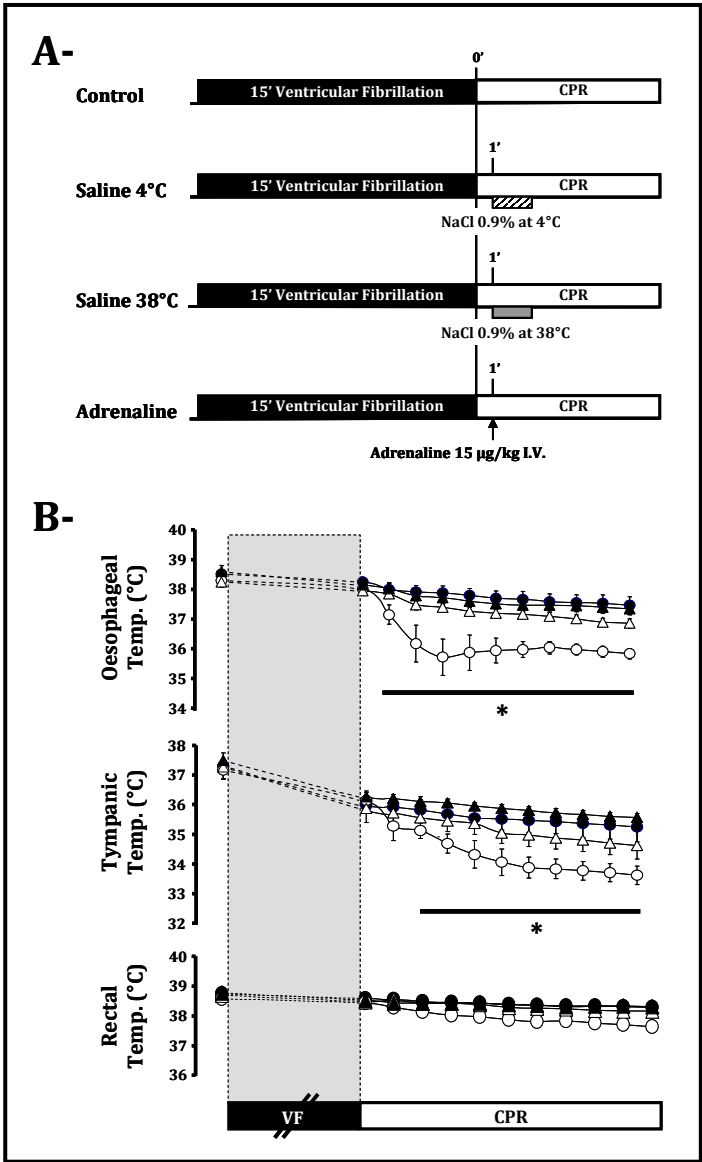
Panel A: Contraction of the aorta rings in response to increasing concentrations of noradrenaline (tension expressed in g).

360 *Panel B: Vasodilating response to acetylcholine and sodium nitroprusside (expressed*
361 *in % of the maximal contraction induced by noradrenaline).*

362 **, $p < 0.05$ vs Sham at the same temperature.*

363

364 **Figure 1**
365



366 **Figure 2**
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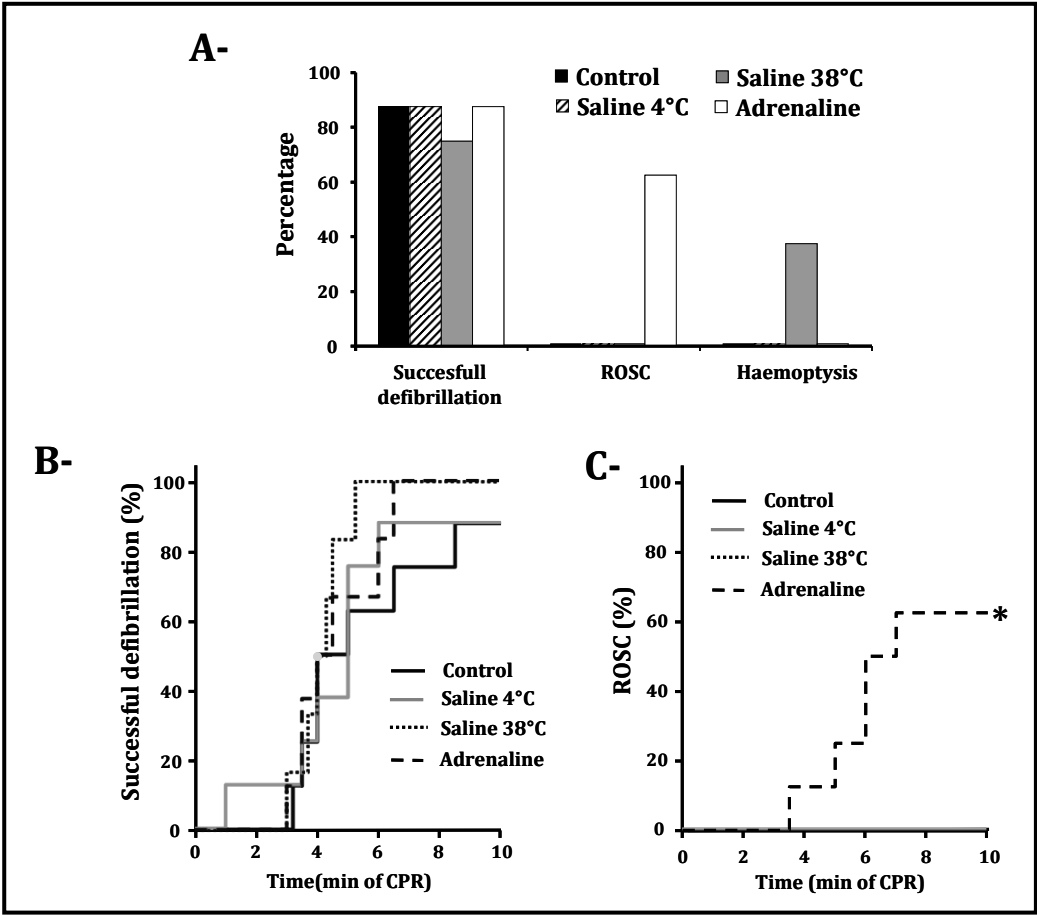


Figure 3

